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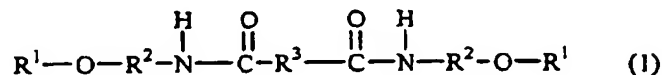
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(54) EXTERNAL PREPARATION COMPOSITIONS

(57) The present invention relates to a dermatologic preparation containing a diamide derivative represented by the following formula (1):



(wherein, R¹ represents a linear or branched hydrocarbon group having 1 to 22 carbon atoms which may be substituted by one or more hydroxy and/or alkoxy groups, R² represents a linear or branched divalent hydrocarbon group having 1 to 12 carbon atoms, and R³ represents a linear or branched divalent hydrocarbon group having 1 to 42 carbon atoms). This diamide derivative (1) is capable of fundamentally improving the water retention capacity and barrier functions of the horny layer, is excellent in miscibility and mixing stability and can be prepared efficiently at a low cost.

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Description

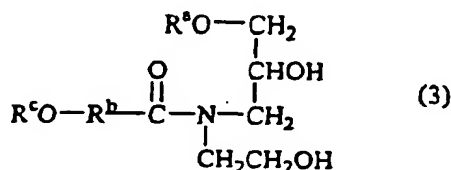
Technical Field

[0001] The present invention relates to dermatologic preparations capable of exerting excellent effects of maintaining normal barrier functions of the horny layer, restoring and reinforcing damaged barrier functions, heightening water retention of the horny layer and remedying skin chapping; and novel diamide derivatives having such effects.

Background Art

[0002] When the water retention capacity or barrier functions of the horny layer are weakened by some internal or external reasons, the skin suffers from troubles such as chapping and acceleration of aging. It is therefore highly important to maintain and reinforce the water retention capacity and barrier functions of the horny layer for our healthy daily life.

[0003] The present applicant has formerly proposed dermatologic preparations comprising an amide derivative represented by the following formula (3):



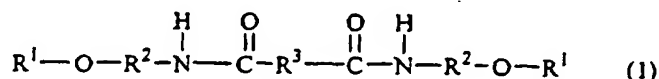
(wherein, R^a represents a linear or branched, saturated or unsaturated hydrocarbon group having 10 to 40 carbon atoms, R^b represents a linear or branched divalent hydrocarbon group having 3 to 39 carbon atoms, R^c represents a hydrogen atom, a linear or branched, saturated or unsaturated hydrocarbon group having 10 to 40 carbon atoms or an acyl group) as a dermatologic preparation capable of essentially improving (maintaining, reinforcing) the barrier functions of the horny layer (Japanese Patent Application Laid-Open (*Kokai*) No. 4-128256).

[0004] Although these amide derivatives exert the above-described excellent effects, they still involve some problems in miscibility or mixing stability because they do not always have sufficient solubility in bases and solution stability. Moreover, preparation of such amide derivatives requires multi-stage reaction, inevitably causing an increase in their production cost.

[0005] An object of the present invention is therefore to provide a compound capable of essentially improving the water retention capacity and barrier functions of the horny layer, having improved miscibility or mixing stability, and being available efficiently at a low cost; and a dermatologic preparation which contains the above-described compound and, by maintaining and reinforcing the water retention capacity and barrier functions of the horny layer, exerts effects of preventing or remedying skin troubles such as chapping, protecting the hair with its penetrated component, improving touch feel of the hair and preventing or remedying chapping of the scalp.

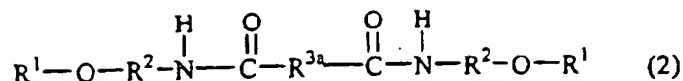
Disclosure of the Invention

[0006] The present invention provides a dermatologic preparation, humectant or skin-barrier-function reinforcing agent, which comprises a diamide derivative represented by the following formula (1):



(wherein R^1 represents, a linear or branched hydrocarbon group having 1 to 22 carbon atoms which may be substituted by one or more hydroxy and/or alkoxy groups, R^2 represents a linear or branched divalent hydrocarbon group having 1 to 12 carbon atoms, and R^3 represents a linear or branched divalent hydrocarbon group having 1 to 42 carbon atoms).

[0007] The present invention also provides a diamide derivative represented by the following formula (2):



(wherein, R¹ represents a linear or branched hydrocarbon group having 1 to 22 carbon atoms which may be substituted by one or more hydroxy and/or alkoxy groups, R² represents a linear or branched divalent hydrocarbon group having 1 to 12 carbon atoms, and R^{3a} represents an alkylene group or an alkenylene group having 1 to 4 double bonds, which alkylene or alkenylene group may be linear or branched and has 11 to 42 carbon atoms).

Best Mode for Carrying out the Invention

[0008] In the diamide derivatives (1) and (2), preferred as R¹ are linear or branched C₁₋₂₂ alkyl groups which may have 1 to 3 substituents selected from a hydroxy group and C₁₋₆ alkoxy groups. Of these, C₁₋₁₈ alkyl groups, C₁₋₁₈ mono- or di-hydroxyalkyl groups, (C₁₋₆ alkoxy-substituted)-(C₁₋₁₈ alkyl) groups, and (hydroxy- and C₁₋₆ alkoxy-substituted)-(C₁₋₁₈ alkyl) groups are preferred, of which C₁₋₁₈ alkyl groups, C₂₋₁₂ mono- or di-hydroxyalkyl groups, (C₁₋₆ alkoxy-substituted)-(C₂₋₁₂ alkyl) groups, and (hydroxy- and C₁₋₆ alkoxy-substituted)-(C₂₋₁₂ alkyl) groups are more preferred. Specific examples include methyl, ethyl, propyl, butyl, hexyl, dodecyl, 2-methylpropyl, 2-ethylhexyl, methyl-branched isostearyl, 2-hydroxyethyl, 9-hydroxynonyl, 2,3-dihydroxypropyl, 2-methoxyethyl, 2-hydroxy-3-methoxypropyl and 9-methoxynonyl groups. Of these, 2-hydroxyethyl, methyl, dodecyl and 2-methoxyethyl groups are more preferred.

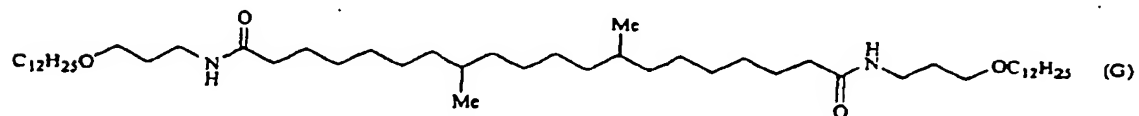
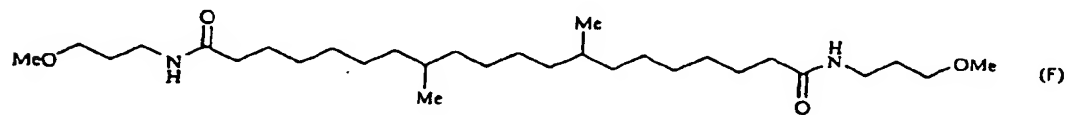
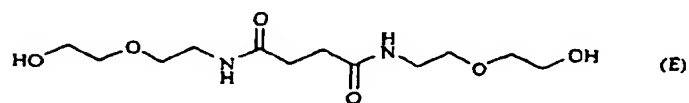
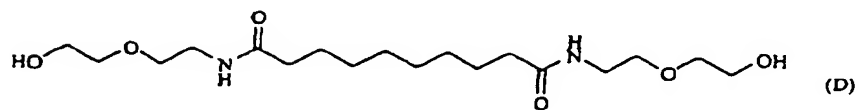
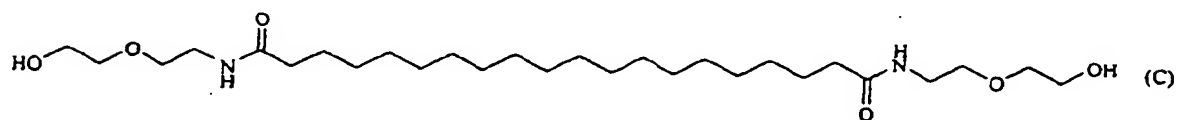
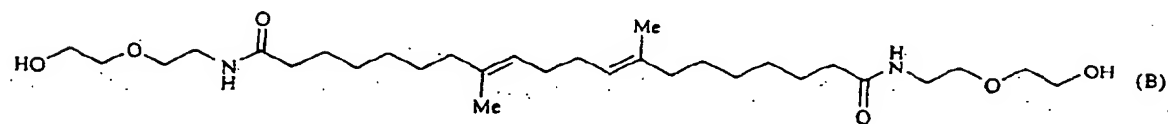
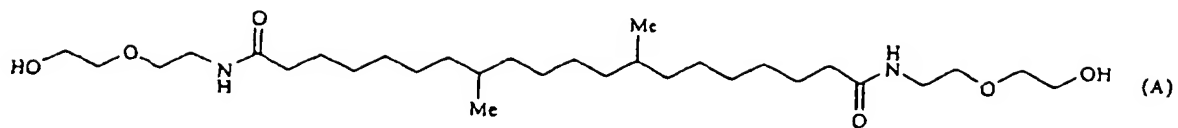
[0009] As R², linear or branched C₁₋₁₂ alkylene groups are preferred, with linear or branched C₂₋₆ alkylene groups being more preferred. Specific examples include ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylenes (ethylidene), 1-methylethylene, 2-methylethylene, 1-methyltrimethylene, 2-methyltrimethylene, 1,1-dimethylethylene and 2-ethyltrimethylene groups, of which ethylene and trimethylene groups are more preferred.

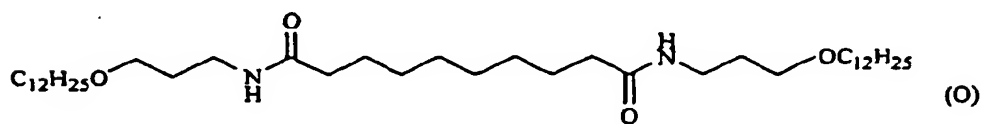
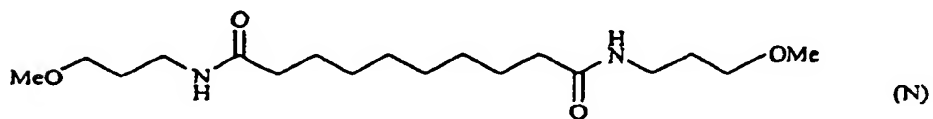
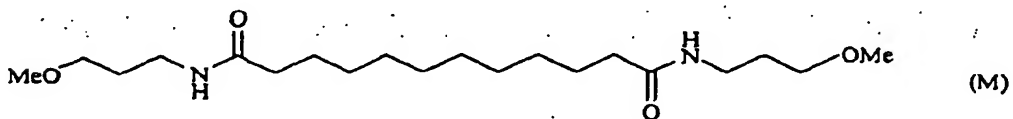
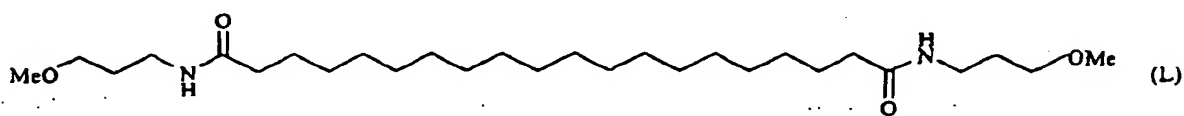
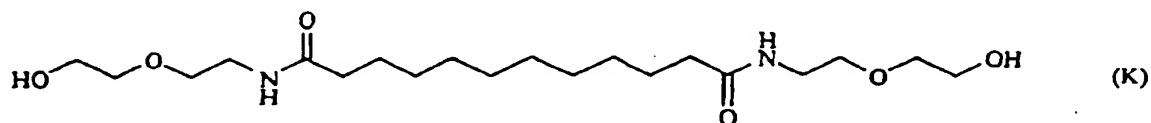
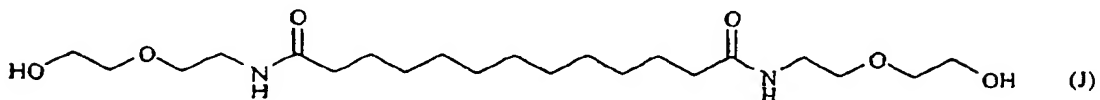
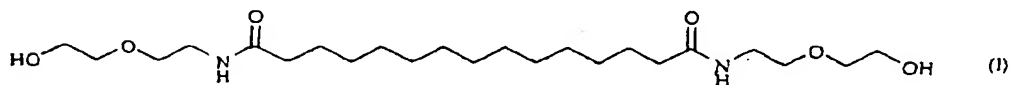
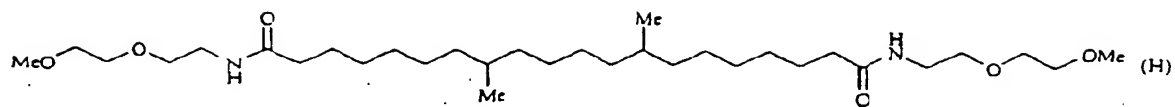
[0010] In the formula (1), linear or branched divalent hydrocarbon groups having 2 to 34 carbon atoms are preferred as R³, with alkylene groups and alkenylene groups having 1 to 4 double bonds each of which may be linear or branched and has 2 to 34 carbon atoms, particularly, alkylene groups and alkenylene groups having 1 to 4 double bonds each of which may be linear or branched and has 2 to 24 carbon atoms being preferred. Specific examples include ethylene, trimethylene, tetramethylene, hexamethylene, heptamethylene, octamethylene, decamethylene, undecamethylene, dodecamethylene, tridecamethylene, tetradecamethylene, hexadecamethylene, octadecamethylene, tricosamethylene, hexacosamethylene, triacontamethylene, 1-methylethylene, 2-ethyltrimethylene, 1-methylheptamethylene, 2-methylheptamethylene, 1-butylhexamethylene, 2-methyl-5-ethylheptamethylene, 2,3,6-trimethylheptamethylene, 6-ethyldecamethylene, 7-methyltetradecamethylene, 7-ethylhexadecamethylene, 7,12-dimethyloctadecamethylene, 8,11-dimethyloctadecamethylene, 7,10-dimethyl-7-ethylhexadecamethylene, 1-octadecylethylene, 9,10-dioctyloctadecamethylene, 8,9-dinonylhexadecamethylene, ethenylene, 1-octadecenylethylene, 7,11-octadecadienylene, 7-ethenyl-9-hexadecamethylene, 7,12-dimethyl-7,11-octadecadienylene, 8,11-dimethyl-7,11-octadecadienylene, 9,10-dioctyl-7,11-octadecadienylene and 8,9-dinonyl-6,10-hexadecadienylene groups. Of these, 7,12-dimethyloctadecamethylene, 7,12-dimethyl-7,11-octadecadienylene, octadecamethylene, octamethylene, decamethylene, undecamethylene and tridecamethylene groups are more preferred.

[0011] In the formula (2), preferred as R^{3a} are alkylene groups and alkenylene groups having 1 to 4 double bonds each of which may be linear or branched and has 12 to 34 carbon atoms, with alkylene groups and alkenylene groups having 1 to 4 double bonds each of which may be linear or branched and has 12 to 24 carbon atoms being more preferred. Of these, 7,12-dimethyloctadecamethylene, 7,12-dimethyl-7,11-octadecadienylene, octadecamethylene and tridecamethylene groups are still more preferred.

[0012] In the diamide derivatives (2) of the present invention, particularly preferred are compounds of the formula (2) having, as R¹, R² and R^{3a}, the groups within the above-described more preferred ranges in combination, respectively. In the diamide derivatives (1) to be used for the dermatologic preparations of the present invention, particularly preferred are compounds of the formula (1) having, as R¹, R² and R³, groups within the above-described more preferred ranges in combination, respectively.

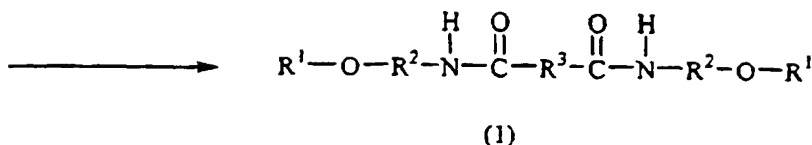
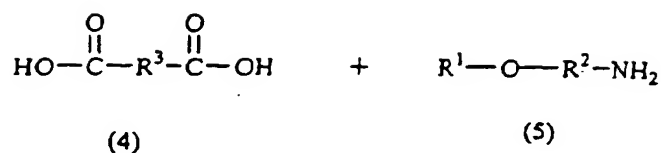
[0013] Particularly preferred examples of the diamide derivatives (1) to be used for the dermatologic preparations of the present invention include:





50 [0014] Particularly preferred examples of the diamide derivatives (2) of the present invention include the above-exemplified compounds (A) to (C), (F) to (J) and (L).

[0015] The diamide derivatives (1) to be used for the dermatologic preparations of the present invention can be prepared by a known amide synthesis method. A preparation process, for example, in accordance with the following reaction scheme can efficiently yield them at a low cost.



(wherein, R¹, R² and R³ have the same meanings as described above).

[0016] The target diamide derivative (1) is available efficiently by condensing a corresponding carboxylic acid (4) or reactive derivative thereof (ester, acid halide or acid anhydride) with an amine (5). This condensation is preferably conducted in the presence or absence of a dehydrating agent such as dicyclohexylcarbodiimide, or a base, for example, an alkali metal hydroxide such as potassium hydroxide or sodium hydroxide, an alkaline earth metal hydroxide such as calcium hydroxide, an alkali metal carbonate such as potassium carbonate, an alkali earth metal carbonate such as calcium carbonate, an alkali metal alcoholate such as sodium methoxide, sodium ethoxide or potassium-tert-butoxide or a tertiary amine such triethylamine or pyridine under a pressure ranging from normal pressure to reduced pressure at 1.3 Pa at room temperature to 250°C. Upon condensation, the amine (5) is preferably used in an excess amount, more specifically, 2 equivalents or greater of the dicarboxylic acid (4) or reactive derivative thereof. For rapid progress of the reaction, it is preferred to conduct the reaction while removing, out of the system, water or an alcohol generated by the reaction. The diamide derivative (1) thus available can be purified in a known manner such as washing with water, column chromatography, distillation, crystallization, recrystallization or powder treatment. Since the diamide derivative (1) obtained in such a manner has effects of penetrating into the lipid layer of the horny layer, thereby maintaining and improving the water retention capacity and barrier functions of the horny layer, it is useful as a humectant or skin-barrier-function reinforcing agent.

[0017] The dermatologic preparations of the present invention are obtained by incorporating the amide derivative (1) in a base (carrier) ordinarily employed for dermatologic preparations. They can be prepared by mixing necessary raw materials in a known manner.

[0018] The dermatologic preparations of the present invention may be broadly classified into medicinal dermatologic preparations and cosmetics depending on the applications thereof. Examples of the medicinal dermatologic preparations include various ointments containing pharmaceutically effective ingredients. These ointments may contain either an oily base or an O/W or W/O emulsion base. No particular limitation is imposed on the oily base and examples thereof include vegetable oils, animal oils, synthetic oils, fatty acids and natural and synthetic glycerides. No particular limitation is imposed on the pharmaceutically effective ingredients and examples thereof include analgesic antiinflammatory agents, antipruritic agents, bactericides, astringents, skin emollients and hormones as needed.

[0019] When the dermatologic preparations of the present invention are used as cosmetics (including skin cosmetics and hair cosmetics), the essential ingredient, that is, the diamide derivative (1), may be arbitrarily blended with commonly used oleaginous components, surfactants, humectants, ultraviolet absorbers, whitening agents, anti-wrinkle compositions, alcohols, chelating agents, pH regulators, antiseptics, thickeners, colorants and perfumes.

[0020] These cosmetics may be formulated into various forms such as W/O and O/W emulsion cosmetics, cream, cosmetic milky lotion, cosmetic lotion, oily cosmetic, lipstick, foundation, bath agent, skin cleanser, nail treatment and hair cosmetics. No particular limitation is imposed on the hair cosmetics and examples include hair tonic, hair dressing, hair rinse, hair treatment, hair conditioner, hair styling agent, shampoo, hair nourishment and hair growth stimulant.

[0021] Although there is no particular limitation imposed on the content of the diamide derivative (1) in the dermatologic preparation of the present invention. In the case of an emulsion type dermatologic preparation, 0.001 to 50 wt. % (which will hereinafter be described % simply) based on the whole composition is preferred. In the case of an oily dermatologic preparation containing a liquid hydrocarbon such as squalane as a base, 0.01 to 50% based on the whole composition is preferred. In either case, 0.01 to 20% is particularly preferred. Particularly, for prevention or remedy of chapping, addition of 0.1 to 20% is preferred. Use of the dermatologic preparation as skin cosmetics is particularly preferred.

[0022] When the dermatologic preparations of the present invention serve as a medicinal dermatologic preparation or skin cosmetic, surfactants such as nonionic surfactants, anionic surfactants, cationic surfactants and amphoteric

surfactants may be incorporated. Of these, nonionic surfactants such as polyoxyethylene alkyl ethers, polyoxyethylene fatty acid esters, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, fatty acid monoglycerides and glyceryl ethers are preferred. As its content, 0.01 to 20%, particularly 0.1 to 10% in the whole preparation is preferred.

[0023] Although no particular limitation is imposed on the content of the diamide derivative (1) in the hair cosmetic of the present invention, preferred is 0.001 to 5% for shampoo, 0.1 to 20% for rinse, treatment, conditioner or styling agent and 0.01 to 5% for hair liquid or hair tonic.

[0024] The hair cosmetic of the present invention may contain surfactants such as anionic surfactants, cationic surfactants, nonionic surfactants and amphoteric surfactants and in addition, components ordinarily employed for hair cosmetics. When the hair cosmetic of the present invention is a shampoo, it may contain, as a main active agent, an anionic surfactant such as an alkyl ether sulfate, alkyl sulfate or olefin sulfonate. As its content, 5 to 30%, particularly 10 to 20%, each based on the whole composition, is preferred.

[0025] When the cosmetic of the present invention is a hair rinse, conditioner, hair treatment or hair styling agent, it may contain a cationic surfactant such as mono- or di-(long chain alkyl) tetraammonium salt, a nonionic surfactant such as polyoxyethylene alkyl or alkenyl ether or an oil/fat such as liquid paraffin for imparting the hair with good touch feel. The content of the cationic or nonionic surfactant is preferably 0.1 to 50%, particularly 0.5 to 20% in the whole composition.

[0026] When the hair cosmetic is a hair liquid or hair tonic, it may contain a nonionic surfactant such as polyoxyethylene. The nonionic surfactant is preferably added in an amount of 0.01 to 20%, particularly 0.1 to 5% in the whole composition.

[0027] The skin cosmetic or hair cosmetic of the present invention containing the diamide derivative (1) may be formulated into an aqueous solution, ethanol solution, emulsion, suspension, gel, solid, aerosol or powder without any limitation.

Examples

Preparation Example 1

Preparation of Compound (A)

[0028] In a flask equipped with a stirrer, a nitrogen inlet tube and a distilling tube, 150 g of dimethyl 8,13-dimethyleicosanedioate ("IPS-22M", product of Okamura Seiyu), 159 g of diglycolamine and 7.5 g of sodium methoxide were charged. The mixture was stirred for 5 hours at 140°C under reduced pressure (20 torr), while distilling off the methanol by-produced. After completion of the reaction, excess diglycolamine was distilled off under reduced pressure. The residue was then washed with water, whereby 200 g (yield: 98%) of the title compound was obtained. The resulting compound 1 (A) has following physical properties:

Colorless paste

¹H-NMR (CDCl₃, δ): 0.67-0.91 (m, 6H), 0.93-1.58 (m, 26H), 1.59-1.76 (m, 4H), 2.17 (t, J=7.2 Hz, 4H), 2.72-3.12 (m, 2H), 3.33-3.52 (m, 4H), 3.52-3.64 (m, 8H), 3.65-3.85 (m, 4H), 6.13-6.56 (m, 2H).

Preparation Examples 2 to 15

[0029] In a similar manner to Example 1 except for the use of the dicarboxylic acid (4) or reactive derivative thereof and, as the amine (5), the compound shown in Table 1 or 2, Compounds (B) to (O) were obtained. These raw materials are shown in Tables 1 and 2, together with the physical properties of the diamide derivatives.

Table 1

	Diamide derivative (1) prepared	Dicarboxylic acid (4) or reactive derivative thereof	Amine (5)	Physical properties
Prep. Ex. 2	Compound (B)	Dimethyl 7,12-dimethyl- 7,11-octadecadiene- 1,18-dicarboxylate ("IPU-22MM", product of Okamura Seiyu)	Diglycolamine	Colorless paste ¹ H-NMR (CDCl ₃ , δ): 1.05-1.45 (m,16H), 1.45-1.72 (m,8H), 1.79-2.08 (m,6H), 2.14 (t,J=7.8Hz,4H), 2.83-3.15 (m,2H), 3.32-3.47 (m,4H), 3.47-3.61 (m,8H), 3.61-3.78 (m,4H), 4.52-5.19 (m,2H), 6.26-6.58 (m,2H).
Prep. Ex. 3	Compound (C)	Dimethyl eicosanedioate ("SL- 20MM", product of Okamura Seiyu)	Diglycolamine	White crystals, Melting point: 135°C ¹ H-NMR (MeOH-d ₄ , δ): 1.18-1.44 (m,28H), 1.48-1.71 (m,4H), 2.18 (t,J=7.4Hz,4H), 3.31-3.43 (m,4H), 3.46-3.60(m,8H), 3.60-3.71(m,4H), 4.49-4.68(m,2H).
Prep. Ex. 4	Compound (D)	Dimethyl sebacate	Diglycolamine	White solid, Melting point: 107°C ¹ H-NMR (CDCl ₃ , δ): 1.22-1.40(m,8H), 1.54-1.72(m,4H),2.19 (t,J=7.2Hz,4H), 2.70-2.90 (m,2H), 3.36-3.54 (m,4H), 3.54-3.70 (m,8H), 3.70-3.89 (m,4H), 6.13-6.30 (m,2H).
Prep. Ex. 5	Compound (E)	Dimethyl succinate	Diglycolamine	White crystals, Melting point: 85°C ¹ H-NMR (CDCl ₃ , δ): 2.52 (s,4H), 3.30-3.50 (m,4H), 3.50-3.64 (m, 8H), 3.64-3.88 (m, 4H), 7.12-7.33 (m, 2H).

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Table 1 (continued)

	Diamide derivative (1) prepared	Dicarboxylic acid (4) or reactive derivative thereof	Amine (5)	Physical properties
Prep. Ex. 6	Compound (F)	Dimethyl 8,13-dimethyleicosane- dioate ("IPS-22MM", product of Okamura Seiyu)	3-Methoxy- propylamine	Colorless paste ¹ H-NMR (CDCl ₃ , δ): 0.67-0.95(m,6H), 1.00-1.48 (m,26H), 1.48-1.70 (m,4H), 1.70-1.88 (m,4H), 2.14 (t,J=7.2Hz,4H), 3.23-3.41 (m,10H), 3.41-3.58 (m,4H), 5.96-6.20 (m,2H).
Prep. Ex. 7	Compound (G)	Dimethyl 8,13-dimethyleicosane- dioate ("IPS-22MM", product of Okamura Seiyu)	3-Dodecyloxy- propylamine	White crystals, Melting point: 36°C ¹ H-NMR (CDCl ₃ , δ): 0.64-0.98 (m,12H), 0.98-1.46 (m,62H), 1.46-1.70 (m,8H), 1.70-1.88 (m,4H), 2.14 (t,J=7.2Hz,4H), 3.26-3.47 (m,8H), 3.47-3.61 (m,4H), 6.09-6.34 (m,2H).
Prep. Ex. 8	Compound (H)	Dimethyl 8,13-dimethyleicosane- dioate ("IPS-22MM", product of Okamura Seiyu)	2-(2-Methoxy- ethoxy)-ethylamine	Colorless paste ¹ H-NMR (CDCl ₃ , δ): 0.69-0.88(m,6H), 0.93-1.41 (m,26H), 1.49-1.68(m,4H), 2.27 (t,J=7.2Hz,4H), 3.36 (s,6H), 3.40-3.68(m, 16H), 5.88-6.06(m, 2H).

Table 2

	Diamide derivative (1) prepared	Dicarboxylic acid (4) or reactive derivative thereof	Amine (5)	Physical properties
Prep. Ex. 9	Compound (I)	Dimethyl pentadecanedioate	Diglycolamine	White crystals, Melting point: 127°C ¹ H-NMR (MeOH-d ₄ , δ): 1.20-1.45 (m,18H), 1.45-1.75 (m,4H), 2.18 (t,J=7.4Hz,4H), 3.25-3.45 (m,8H), 3.52 (t,J=5H.1Hz,4H), 3.60-3.75 (m,4H), 4.60-4.70(m,2H).

Table 2 (continued)

	Diamide derivative (1) prepared	Dicarboxylic acid (4) or reactive derivative thereof	Amine (5)	Physical properties
Prep. Ex.10	Compound (J)	Dimethyl brassylate	Diglycolamine	White crystals, Melting point: 120°C ¹ H-NMR (MeOH-d ₄ , δ): 1.20-1.45 (m,14H), 1.50-1.70 (m,4H), 2.18 (t,J=7.4Hz,4H), 3.25-3.45 (m,8H), 3.52 (t,J=5.0Hz,4H), 3.60-3.75 (m,4H), 4.60-4.70 (m,2H).
Prep. Ex.11	Compound (K)	Dimethyl dodecanedioate	Diglycolamine	White solid, Melting point: 118°C ¹ H-NMR (MeOH-d ₄ , δ): 1.20-1.45 (m,12H), 1.45-1.75 (m,4H), 2.18 (t,J=7.4Hz,4H), 3.25-3.45 (m,8H), 3.52 (t,J=5.1Hz,4H), 3.60-3.75 (m,4H), 4.60-4.70 (m,2H).
Prep. Ex.12	Compound (L)	Dimethyl Eicosanedioate	3-Methoxy- propylamine	White crystals, Melting point: 134 °C ¹ H-NMR (CDCl ₃ , δ): 1.15-1.40 (m,32H), 1.52-1.70 (m,4H), 1.77 (quintet, J=6.1Hz,4H), 2.15 (t,J=7.6Hz,4H), 3.30-3.43 (m,4H), 3.35 (s,6H), 3.48 (t, J=5.7Hz,4H), 5.90-6.10 (m,2H).
Prep. Ex. 13	Compound (M)	Dimethyl dodecanedioate	3-Methoxy- propylamine	White crystals, Melting point: 129°C ¹ H-NMR (CDCl ₃ , δ): 1.15-1.40 (m, 12H), 1.50-1.70(m,4H), 1.70-1.90 (m,4H), 2.15 (t,J=6.1Hz,4H), 3.30-3.45 (m,4H), 3.35 (s,6H), 3.48 (t, J=5.8Hz,4H), 5.95-6.05 (m,2H).